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Observation of flow variation in capillaries of artificial blood vessel by producing microbubble aggregations

微小気泡の凝集体形成による人工血管狭小部における流れの変化とその観測

Nobuhiko Shigehara[1‡], Nobuyuki Watarai[1], Ren Koda[1], Kohji Masuda[1], Yoshitaka Miyamoto[2], and Toshio Chiba[2]

([1] Tokyo University of Agriculture and Technology; [2] National Center for Child Health and Development.)

重原伸彦[1‡], 渡會展之[1], 江田廉[1], 桝田晃司[1], 宮本義孝[2], 千葉敏雄[2]

([1] 東京農工大学; [2] 国立成育医療研究センター)

1. Introduction

Making use of the phenomena that microbubbles of μm order collapse under ultrasound emission near their resonant frequency, various types of therapeutic application have been proposed[1]. By utilizing the effect of microbubble sonoporation, which allows uptake of many molecules into the cell, new methods for drug delivery, gene delivery and improvement of the efficiency of High Intensity Focused Ultrasound therapy (HIFU) are expected[2,3]. In addition, microbubbles are known to form aggregations under ultrasound emission because of the secondary bjerknes force[4]. We have reported our attempt using the suspension of bubbles with actual RBCs to investigate trapping performance of bubbles[5]. Also we have elucidated the conditions of ultrasound and flow velocity for active path selection of aggregations of bubbles in an artificial blood vessel[6]. However, blood vessels and capillaries have a complex structure and our early attempts are unclear *in vivo*. In this paper, we observed flow variation in capillaries of artificial blood vessel by producing microbubble aggregations.

2. Theory

Assuming spherical bubbles, a secondary bjerknes force acts under the ultrasound emission. If two bubbles are located in an even ultrasound emission and oscillate, the secondary bjerknes force between the bubbles F is defined as

$$\langle F \rangle = -\frac{2\pi\rho R_{10}^3 R_{20}^3 \omega^2}{D^2} \varepsilon_{10}\varepsilon_{20}\cos(\varphi_1 - \varphi_2), \qquad (2)$$

where symbol of < > means time integration of the driven ultrasound emission in one period, ρ is the density of the liquid, R_{10} and R_{20} are initial radius of the bubble 1 and 2, ε_{10} and ε_{20} are oscillation amplitude of the bubblle 1 and 2, ω is angular frequency, D is the distance between bubbles, and ϕ_1 - ϕ_2 are the phase differences of the oscillation between bubbles, respectively.

When the microbubble aggregations are placed in a water flow, a driving force of flow affects aggregations. **Figure 1** shows process of microbubble aggregations in capillaries of artificial blood vessel. First, aggregations are formed by the secondary bjerknes force and flow both to path (a) and path (b). Second, aggregations flowing to path (b) enter the capillaries and the aggregations whose diameter is larger than the width of the capillary are blocked. Third, waterflow to path (b) is blocked by the clining aggregations, and aggregations flow to path (a)

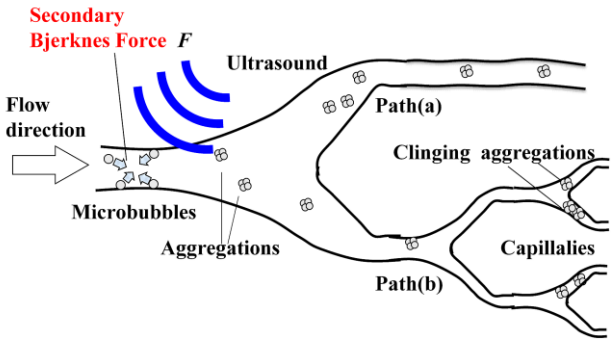

Fig. 1 Process of microbubble aggregations of capillaries in artificial blood vessel.

3. Experiment

Figure 2 shows the experimental setup and the artificial blood vessel. In this experiment, the microbubble Sonazoid® which has a phospholipid shell and perfulbutane inside with average diameter from 2 to 3 μm is used. To observe the behavior of the microbubble aggregations with the secondary bjerknes force, we prepared artificial blood vessel with a branch, which is made of poly (ethylene glycol). Moreover, a sponge which has architecture of capillary following the branch is inserted. The energy of ultrasound in water reaches the path with high efficiency since the acoustic impedance of poly (ethylene glycol) (sound velocity: 1540-1560 m/s, density: 1.27 g/mL) is similar to that of water. The angle of the axis of the transducer as 60 deg is

set and focal point of ultrasound emission corresponds from the sponge 2 mm. The vessel is fixed 23 mm floated from the bottom of water tank, which is filled with water, to guarantee the working distance of the optical microscope (Omron KH-7700) to observe the path through the transparent bottom plate of the tank.

We have to mention that we have confirmed the aggregations clinging on the sponge is larger, bubbles of flow change from path (a) to path (b).

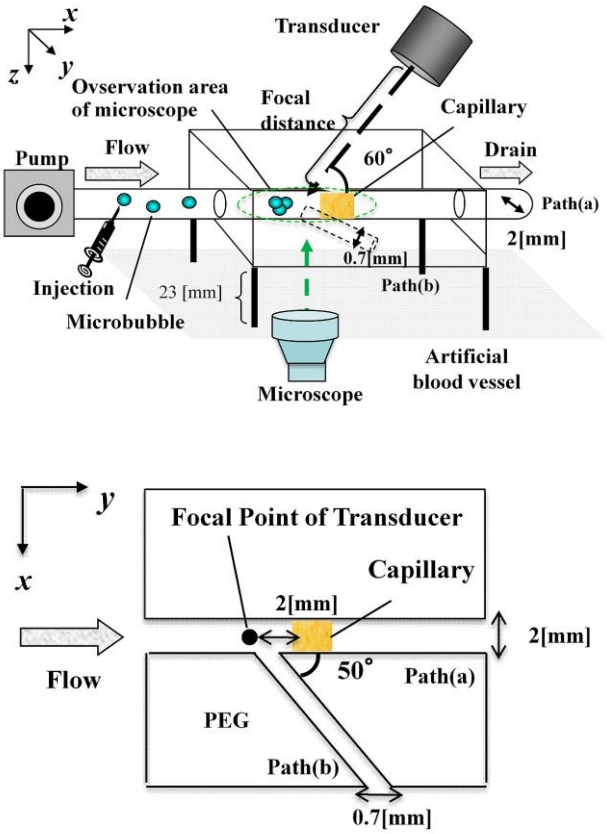

Fig. 2 Experimental setup and structure of artificial blood vessel.

4. Results

Figure 3 shows behavior of aggregations in observation area under continuous ultrasound emission of central frequency 3 MHz and sound pressure 300 kPa with flow velocity 20 mm/s. It is confirmed that the area of aggregations clinging on the sponge increased according to emission time proportionally. Moreover, when area of aggregations clinging on the sponge is large, water flow to path (a) is blocked and the influence of the flow of the path (b) grows larger. New formed aggregations can flow to the path (b). This shows dot-circle lines, which are the microbubble aggregations flowing to path (b) in Fig. 3. From these results, microbubble aggregations were clinging on the sponge by degree on time and entering to path (b) between 20.7-and 30.2 [s], 30.2-and 40.3 [s] also 47.8 and 51.1 [s].

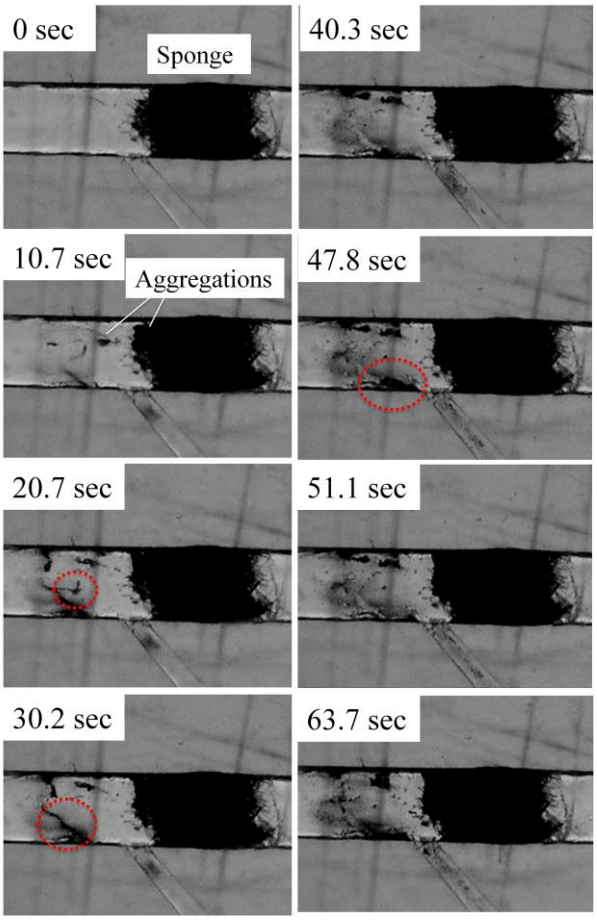

Fig. 3 Behavior of aggregations in observation area under continuous ultrasound emission of central frequency 3 MHz and sound pressure 300 kPa with flow velocity 20 mm/s.

5. Conclusions

In this study, we observed microbubble aggregations in artificial blood vessel which has capillaries. We confirmed that when aggregations clinging on the capillary were large, it blocked water flow. If area of the aggregations can be controlled, actual blood vessels might be blocked on purpose using an ultrasound and aggregations. Also we are going to apply to *in vivo* experiment.

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